

CLAIMS

What is claimed is:

1. A method for treating a human having a disease associated with leukocyte infiltration of mucosal tissues, comprising administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for $\alpha 4\beta 7$ integrin, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an antibody of human origin, wherein said immunoglobulin or fragment is administered in an initial dose followed by one or more subsequent doses and the minimum interval between any two doses is a period of at least about 1 day, and wherein no more than about 8 mg immunoglobulin or fragment per kg body weight are administered during a period of about one month.
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2. The method of Claim 1 wherein said immunoglobulin or fragment binds the $\alpha 4$ chain of $\alpha 4\beta 7$ integrin.
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15 3. The method of Claim 1 wherein said immunoglobulin or fragment binds the $\beta 7$ chain of $\alpha 4\beta 7$ integrin.
4. The method of Claim 1 wherein said immunoglobulin or fragment has binding specificity for the $\alpha 4\beta 7$ complex.
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5. The method of Claim 1 wherein said portion of an immunoglobulin of human origin is derived from a human constant region.
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6. The method of Claim 5 wherein said antigen binding region is of rodent origin.

7. The method of Claim 1 wherein said antigen binding region comprises a complementarity determining region of rodent origin, and said portion of an antibody of human origin is derived from a human framework region.

8. The method of Claim 1 wherein said antigen binding region comprises at least one of three complementarity determining regions (CDR1, CDR2 and CDR3) of a light chain variable region and at least one of three complementarity determining regions (CDR1, CDR2 and CDR3) of a heavy chain variable region of the amino acid sequence set forth below:

light chain: CDR1 SEQ ID NO: 9
10 CDR2 SEQ ID NO: 10
CDR3 SEQ ID NO: 11
heavy chain: CDR1 SEQ ID NO: 12
CDR2 SEQ ID NO: 13
CDR3 SEQ ID NO: 14.

15 9. The method of Claim 8 wherein said antigen binding region comprises three complementarity determining regions (CDR1, CDR2 and CDR3) of a light chain variable region and three complementarity determining regions (CDR1, CDR2 and CDR3) of a heavy chain variable region of the amino acid sequence set forth below:

20 light chain: CDR1 SEQ ID NO: 9
CDR2 SEQ ID NO: 10
CDR3 SEQ ID NO: 11
heavy chain: CDR1 SEQ ID NO: 12
CDR2 SEQ ID NO: 13
CDR3 SEQ ID NO: 14.

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10. The method of Claim 1 wherein said humanized immunoglobulin or antigen-binding fragment thereof comprises a heavy chain and a light chain,
the light chain comprising complementarity determining regions derived
from an antibody of nonhuman origin which binds $\alpha 4\beta 7$ and a framework
5 region derived from a light chain of human origin, wherein each of said
complementarity determining regions (CDR1, CDR2 and CDR3) comprises the
amino acid sequence set forth below:

light chain: CDR1 SEQ ID NO: 9
CDR2 SEQ ID NO: 10
10 CDR3 SEQ ID NO: 11; and

the heavy chain comprising complementarity determining regions
derived from an antibody of nonhuman origin which binds $\alpha 4\beta 7$ and a
framework region derived from a heavy chain of human origin, wherein each of
said complementarity determining regions (CDR1, CDR2 and CDR3) comprises
15 the amino acid sequence set forth below:

heavy chain: CDR1 SEQ ID NO: 12
CDR2 SEQ ID NO: 13
CDR3 SEQ ID NO: 14.

11. The method of Claim 10 wherein said humanized immunoglobulin or antigen-binding fragment thereof comprises the heavy chain variable region of SEQ ID
20 NO:6.

12. The method of Claim 10 wherein said humanized immunoglobulin or antigen-binding fragment thereof comprises the light chain variable region of SEQ ID
NO:8.

13. The method of Claim 1 wherein each of said doses independently comprise about 0.1 to about 8 mg immunoglobulin or fragment per kg body weight.
14. The method of Claim 1 wherein each of said doses independently comprise about 0.1 to about 5 mg immunoglobulin or fragment per kg body weight.

5 15. The method of Claim 1 wherein each of said doses independently comprise about 0.1 to about 2.5 mg immunoglobulin or fragment per kg body weight.

16. The method of Claim 1 wherein each of said doses independently comprise about 0.15, about 0.5, about 1.0, about 1.5 or about 2.0 mg immunoglobulin or fragment per kg body weight.

10 17. The method of Claim 1 wherein the interval between doses is at least about 7 days.

18. The method of Claim 1 wherein the interval between doses is at least about 14 days.

15 19. The method of Claim 1 wherein the interval between doses is at least about 21 days.

20. The method of Claim 1 wherein the interval between doses is at least about 28 days.

20 21. The method of Claim 1 wherein the interval between doses is at least about 30 days.

22. The method of Claim 1 wherein said each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve a) about 50% or greater saturation of $\alpha 4\beta 7$ integrin binding sites on circulating lymphocytes and/or b) about 50% or greater inhibition of $\alpha 4\beta 7$ integrin expression on the cell surface of circulating lymphocytes, and wherein said saturation and/or inhibition is maintained for a period of at least about 10 days following administration of said dose.
5. 23. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve a) about 60% or greater saturation of $\alpha 4\beta 7$ integrin binding sites on circulating lymphocytes and/or b) about 60% or greater inhibition of $\alpha 4\beta 7$ integrin expression on the cell surface of circulating lymphocytes.
10. 24. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve a) about 70% or greater saturation of $\alpha 4\beta 7$ integrin binding sites on circulating lymphocytes and/or b) about 70% or greater inhibition of $\alpha 4\beta 7$ integrin expression on the cell surface of circulating lymphocytes.
15. 25. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve a) about 80% or greater saturation of $\alpha 4\beta 7$ integrin binding sites on circulating lymphocytes and/or b) about 80% or greater inhibition of $\alpha 4\beta 7$ integrin expression on the cell surface of circulating lymphocytes.
20. 26. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve and

maintain said saturation and/or inhibition for a period of at least about 14 days following administration of said dose.

27. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve and maintain said saturation and/or inhibition for a period of at least about 20 days following administration of said dose.
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28. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve and maintain said saturation and/or inhibition for a period of at least about 25 days
10 following administration of said dose.
29. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve and maintain said saturation and/or inhibition for a period of at least about 30 days following administration of said dose.
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30. The method of Claim 22 wherein each of said doses independently comprise an amount of immunoglobulin or fragment which is sufficient to achieve and maintain said saturation and/or inhibition for a period of at least about 60 days following administration of said dose.
31. The method of claim 22 wherein each of said doses independently comprise about 0.1 to about 8 mg immunoglobulin or fragment per kg body weight.
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32. The method of claim 22 wherein each of said doses independently comprise about 0.1 to about 5 mg immunoglobulin or fragment per kg body weight.
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33. The method of claim 22 wherein each of said doses independently comprise about 0.1 to about 2.5 mg immunoglobulin or fragment per kg body weight.
34. The method of Claim 22 wherein each of said doses independently comprise about 0.15, about 0.5, about 1.0, about 1.5 or about 2.0 mg immunoglobulin or fragment per kg body weight.
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35. The method of Claim 22 wherein the interval between doses is at least about 7 days.
36. The method of Claim 22 wherein the interval between doses is at least about 14 days.

10 37. The method of Claim 22 wherein the interval between doses is at least about 21 days.

38. The method of Claim 22 wherein the interval between doses is at least about 28 days.

15 39. The method of Claim 22 wherein the interval between doses is at least about 30 days.

40. The method of Claim 1 wherein a humanized immunoglobulin is administered and each of said doses comprises an amount of immunoglobulin which is sufficient to achieve and maintain a serum concentration of immunoglobulin of at least about 1 µg/mL for a period of at least about 10 days following
20 administration of said dose.

41. The method of Claim 40 wherein each of said doses independently comprise an amount of immunoglobulin which is sufficient to achieve and maintain said serum concentration for a period of at least about 14 days following administration of said dose.
- 5 42. The method of Claim 40 wherein each of said doses independently comprise an amount of immunoglobulin which is sufficient to achieve and maintain said serum concentration for a period of at least about 20 days following administration of said dose.
- 10 43. The method of Claim 40 wherein each of said doses independently comprise an amount of immunoglobulin which is sufficient to achieve and maintain said serum concentration for a period of at least about 25 days following administration of said dose.
- 15 44. The method of Claim 40 wherein each of said doses independently comprise an amount of immunoglobulin which is sufficient to achieve and maintain said serum concentration for a period of at least about 30 days following administration of said dose.
- 20 45. The method of Claim 40 wherein each of said doses independently comprise an amount of immunoglobulin which is sufficient to achieve and maintain said serum concentration for a period of at least about 60 days following administration of said dose.
46. The method of Claim 40 wherein each of said doses independently comprise about 0.1 to about 8 mg immunoglobulin per kg body weight.

47. The method of Claim 40 wherein each of said doses independently comprise about 0.1 to about 5 mg immunoglobulin per kg body weight.
48. The method of Claim 40 wherein each of said doses independently comprise about 0.1 to about 2.5 mg immunoglobulin per kg body weight.
- 5 49. The method of Claim 40 wherein each of said doses independently comprise about 0.15, about 0.5, about 1.0, about 1.5 or about 2.0 mg immunoglobulin or fragment per kg body weight.
50. The method of Claim 40 wherein the interval between doses is at least about 7 days.
- 10 51. The method of Claim 40 wherein the interval between doses is at least about 14 days.
52. The method of Claim 40 wherein the interval between doses is at least about 21 days.
- 15 53. The method of Claim 40 wherein the interval between doses is at least about 28 days.
54. The method of Claim 40 wherein the interval between doses is at least about 30 days.
55. The method of Claim 1 further comprising administering an effective amount of one or more additional therapeutic agents.

56. The method of Claim 55 wherein said agents are selected from the group consisting of steroids, immunosuppressive agents, non-steroidal anti-inflammatory agents and immunomodulators.
57. The method of Claim 55 wherein said agents are selected from the group consisting of azathioprene, 6-mercaptopurine, sulfasalazine, 5-amino salicylic acid, prednisone and prednisolone.
58. The method of Claim 1 wherein said disease associated with leukocyte infiltration of mucosal tissues is selected from the group consisting of an inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma and graft versus host disease.
59. The method of Claim 1 wherein said disease associated with leukocyte infiltration of mucosal tissues is an inflammatory bowel disease.
60. The method of Claim 59 wherein said inflammatory bowel disease is ulcerative colitis.
- 15 61. The method of Claim 59 wherein said inflammatory bowel disease is Crohn's disease.

62. A method for treating a human having inflammatory bowel disease, comprising administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for $\alpha 4\beta 7$ integrin, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an antibody of human origin, wherein said immunoglobulin or fragment is administered in an initial dose followed by one or more subsequent doses and the minimum interval between any two doses is a period of at least about 1 day, and wherein no more than about 8 mg immunoglobulin or fragment per kg body weight are administered during a period of about one month.

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63. The method of Claim 62 wherein said humanized immunoglobulin or antigen-binding fragment thereof comprises a heavy chain and a light chain, the light chain comprising complementarity determining regions derived from an antibody of nonhuman origin which binds $\alpha 4\beta 7$ and a framework region derived from a light chain of human origin, wherein each of said 15 complementarity determining regions (CDR1, CDR2 and CDR3) comprises the amino acid sequence set forth below:

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light chain: CDR1 SEQ ID NO: 9
CDR2 SEQ ID NO: 10
CDR3 SEQ ID NO: 11; and

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the heavy chain comprising complementarity determining regions derived from an antibody of nonhuman origin which binds $\alpha 4\beta 7$ and a framework region derived from a heavy chain of human origin, wherein each of said complementarity determining regions (CDR1, CDR2 and CDR3) comprises the amino acid sequence set forth below:

heavy chain: CDR1 SEQ ID NO: 12
CDR2 SEQ ID NO: 13
CDR3 SEQ ID NO: 14.

64. The method of Claim 63 wherein the inflammatory bowel disease is ulcerative colitis.
65. The method of Claim 63 wherein the inflammatory bowel disease is Crohn's disease.

5 66. A method for inhibiting relapse and/or recurrence of quiescent inflammatory bowel disease in a human, comprising administering to said human an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for $\alpha 4\beta 7$ integrin, said immunoglobulin or fragment comprising an antigen binding region of nonhuman origin and at least a portion of an immunoglobulin of human origin, wherein said immunoglobulin or fragment is administered in doses and the minimum interval between doses is a period of at least about 7 days, and wherein no more than about 8 mg immunoglobulin or fragment per kg body weight are administered during a period of about 30 days.

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15 67. The method of Claim 66 wherein quiescence has been induced by medical or surgical therapy.

68. The method of Claim 66 wherein said inflammatory bowel disease is ulcerative colitis.

20 69. The method of Claim 66 wherein said inflammatory bowel disease is Crohn's disease.